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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Alain Schoueteen et al. Docket: 2003FR302  
Serial No.: 10/584,440 Group Art Unit: 1625  
Filed/371(c) Date: November 29, 2006 Examiner: Chandrakumar, N.  
For: PROCESS FOR THE PREPARATION OF N-ALKYL-2(HYDROXY-  
4BENZOYL)-3 BENZOFURANS AND ITS INTERMEDIATES THEREOF

DECLARATION UNDER 37 CFR 1.132

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Dear Sir:

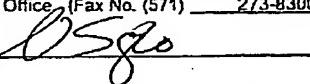
I, Alain Schoueteen, state that I am a resident of rue de Normandie 17, 95460 Ezanville France ; that I am a citizen of France; that I am a chemist having graduated from the 1970 at the Ecole Nationale Supérieure de Chimie de Paris (France). and in 1974 I received a PhD in organic chemistry at the University of Paris VI (France)

I am one of the named inventors and I am acquainted with the subject matter of the above subject Application No. 10/584,440, 371(c) date of November 29, 2006 in the name of Alain Schoueteen et al for "PROCESS FOR THE PREPARATION OF N-ALKYL-2(HYDROXY-4BENZOYL)-3 BENZOFURANS AND ITS INTERMEDIATES THEREOF".

I consider myself qualified, by my knowledge of chemistry, and especially of the chemistry of organic synthesis and by my 34 (thirty four) years of experience in research and development departments of chemical companies.

CERTIFICATE OF MAILING/TRANSMISSION (37 CFR 1.8a) and 1.10

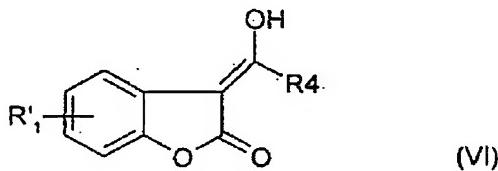
I hereby certify that this correspondence is, on the date shown below, being transmitted by facsimile to the U.S. Patent and Trademark Office, (Fax No. (571) 273-8300) 1 (7) pages.

  
Vicki Sgro

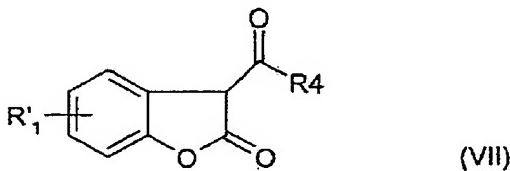
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Page 2  
 Attorney's Docket: 2003FR302  
 Serial No.: 10/584,440  
 Art Unit 1625  
DECLARATION UNDER 37 CFR 1.132

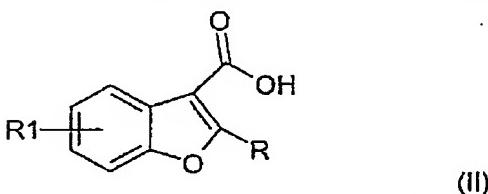
The subject application discloses a process for the preparation of the preparation of a 2-(n-alkyl)-3-carboxybenzofuran of formula (II). According to the claimed process, a 3-(1-hydroxyalkylidene)-3H-benzofuran-2-one of formula (VI):



or its 3-alkanoyl-3H-benzofuran-2-one ketonic tautomeric form of formula (VII):



in which R4 represents a linear or branched alkyl radical including from 2 to 5 carbon atoms and R'1 represents a nitro radical, is treated by heating in the presence of an acid catalyst in concentrated aqueous solution of at least 80% by weight of the acid to provide the 2-(n-alkyl)-3-carboxybenzofuran of formula (II)

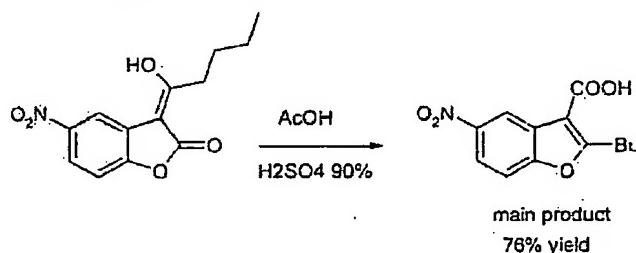


The product is subsequently isolated by conventional means. The following remarks are directed to a side-by side comparison of a publication entitled, "Experiments on the synthesis of Furano Compounds. Part XII. Further Transformations of isocoumaranone," Chatterjea, J.N, Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305(hereinafter referred to as Chatterjea). Chatterjea differs from the instant invention in that the substituents R1' and R4 of the instant invention are not disclosed in the Chatterjea reference.

Page 3  
 Attorney's Docket: 2003FR302  
 Serial No.: 10/584,440  
 Art Unit 1625  
DECLARATION UNDER 37 CFR 1.132

As mentioned page 8 of the description of the subject Application, the compound (VI) "...is treated by heating, preferably in a carboxylic acid , in particular acetic acid , and by an acid catalyst in a concentrated aqueous solution at least 80% by weight..." to form the desired compound (II) which can be isolated. This is exemplified in the example 1 of Applicant's Specification, and summarized hereinbelow:

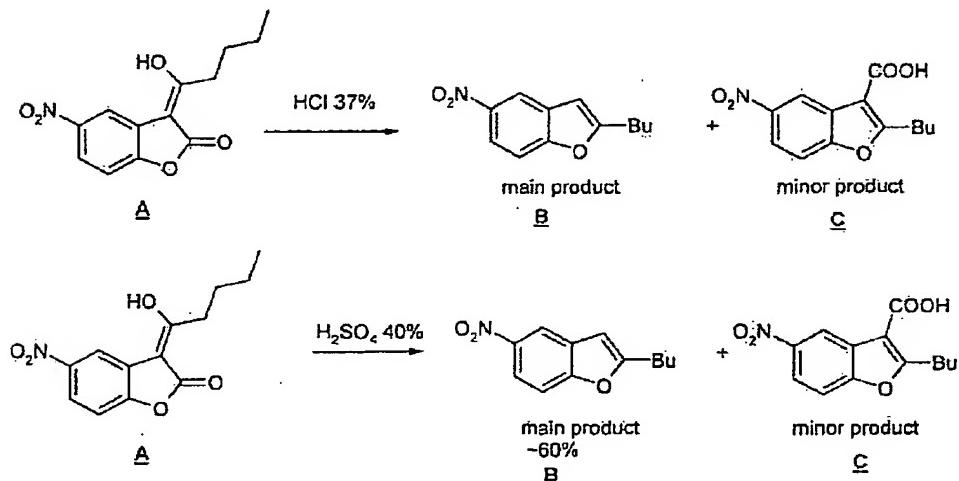
Example 1 : preparation of 2-(n-butyl)-3-carboxy-5-nitrobenzofuran



In the publication of Chatterjea , (Chatterjea (Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305) such reaction is accomplished with different starting materials and other substituents with concentrated HCl , the concentration of which is 37% maximum. Although Chatterjea does not specifically indicate the concentration of the HCl used, Chatterjea does disclose a concentrated HCl solution which means 37% in water (See Experimental, p 301 , second example : 2-o-Methoxybenzylcoumarone-3-carboxylic Acid ). The concentration of 37 weight percent HCl is the concentration of the commercial concentrated aqueous HCl. Higher HCl concentration could be obtained, but this requires solutions under pressure which is not the case here. In the other examples of Chatteerjea, at page 303, 2-Methylcoumarone-3-carboxylic Acid , example (b), Chatterjea mentions HCl (4cc ), and latter in the example at page 305 " Isomerisation of the Self-condensation Product" HCl (1,5 cc ) is also interpreted to mean HCl conc, i.e., 37% according to the previous examples.

Page 4  
 Attorney's Docket: 2003FR302  
 Serial No.: 10/684,440  
 Art Unit 1625  
DECLARATION UNDER 37 CFR 1.132

Applicant discovered that when concentrated HCl is used for the synthesis of (II) from (VI) or (VII), the main product is not the expected product (II) but the product of decarboxylation as well as when diluted sulphuric acid is used.



In order to compare the experiments disclosed in the Chatterjea Publication, the following experiments were carried out to show the influence of the concentration of the acid employed in the reaction:

Influence of the acid catalyst by using operating conditions of Chatterjea

The following experiments were run using the conditions very similar to the conditions disclosed in Chatteja and are shown in Table A:

Table A

Starting material	Acetic acid	Strong acid	operating conditions	Crude yield	
				B	C
example 1	0.875g	25g	25g HCl conc. 37%	59%	9%
example 2	0.876g	25g	28g H <sub>2</sub> SO <sub>4</sub> 42%	51%	3%
example 3	8.68g	61.41g	18.4g H <sub>2</sub> SO <sub>4</sub> 40%	58%	4%

Note: B and C refer to the species shown in the above figure showing the species produced.

Page 5  
 Attorney's Docket: 2003FR302  
 Serial No.: 10/584,440  
 Art Unit 1625  
DECLARATION UNDER 37 CFR 1.132

Experimental procedures which were followed for Experiment 1-3 in Table A are summarized hereinbelow.

**Example 1:**

0.876g of A ( 3.33 mmoles ) were mixed with 25g of acetic acid and 25g of concentrated HCl solution 37%. The resulting mixture was then heated at 102°C during 7 hours. A sample was taken and analyzed by HPLC (High Pressure Liquid Chromatography) for determining the crude yields for species B and C.

**Example 2:**

0.876g of A ( 3.33 mmoles ) were mixed with 25g of acetic acid and with 28.15g of a 44% aqueous sulfuric solution ( i.e., containing 12.4g of concentrated sulfuric acid and 15.75g of water ). The resulting mixture was then heated at 100°C during 3.25 hours. A sample was taken and analyzed by HPLC for determining the crude yields for B and C.

**Example 3 :**

8.68g of A ( 0.033 moles ) were mixed with 61.41g of acetic acid and with 16.175g of a 40% aqueous sulfuric solution ( ie containing 6.47g of concentrated sulfuric acid and 9.705g of water ). The resulting mixture was then heated at 116°C during 7 hours. A sample was taken and analyzed by HPLC for determining the crude yields for B and C

These procedures and conditions can be seen to be very similar to those disclosed in the Chatterjea Publication which are summarized hereinbelow in

**Table B:**

**Table B**

	starting material	Acetic acid	HCl	final products
Chatterjea	example p 301	0.6g	3cc = 3.1g	1cc=1.19g HCl conc no yield given
Chatterjea	example p 303	10.5g	6cc = 6.3g	4cc = 4.76g no yield given

Thus, the results in Table A clearly show that by using HCl conc. 37% as Chatterjea disclosed, that the species B is mainly formed, and that the species C

Page 6  
 Attorney's Docket: 2003FR302  
 Serial No.: 10/584,440  
 Art Unit 1625  
DECLARATION UNDER 37 CFR 1.132

is the minor product . Thus, HCl conc 37% as well as diluted H<sub>2</sub>SO<sub>4</sub> are not suitable reactants for synthesizing a major portion of the species product C.

In order to further emphasize the influence of the acid concentration on the selectivity and yield of the species, a series of further experiments were performed. The effect of the acid concentration on the yield of product species B and product C are shown in Table C, wherein the acid concentration is increased from a level of 20 to 85 weight percent. The procedure for each of the experiments 4-10 is illustrated by the following description of the procedure for Experiment 6:

Example 6 : 9.53g of A ( 36.2 mmoles ) were mixed with 34.75g of acetic acid , and with 11.82g of a 60% aqueous sulfuric acid solution (i.e., containing 7.24g of concentrated sulfuric acid 98% and 4.58g of water ). The resulting mixture was then heated at 118°C during 7 hours. A sample was taken and analyzed by HPLC for determining the crude yields for product species B and product species C.

#### Influence of the concentration of the acid catalyst :

The following table shows the influence of the concentration of the strong acid H<sub>2</sub>SO<sub>4</sub> :

Table C

	H <sub>2</sub> SO <sub>4</sub> Concentration (a)	operating conditions	Crude yield	
			B	C
example 4	85	126°C ; 3.5 hours	14%	65%
example 5	75	118°C ; 6 hours	27%	47%
example 6	60	118°C ; 7 hours	48%	30%
example 7	50	116°C ; 7 hours	59%	12%
example 8	40	116°C ; 8 hours	65%	3%
example 9	30	111°C ; 10 hours	45%	1%
example 10	20	110°C ; 12 hours	34%	0

(a) : concentration of the initial H<sub>2</sub>SO<sub>4</sub> in water

One can clearly see that when increasing the concentration of sulfuric acid, the yields increase for Applicant's desired product species C. Applicant discovered that when the acid concentration is increased above 80 weight percent that the

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AUG 29 2008

Page 7

Attorney's Docket: 2003FR302

Serial No.: 10/584,440

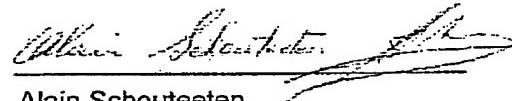
Art Unit 1625

DECLARATION UNDER 37 CFR 1.132

production species C is produced as a major product compared to the acid levels of the Chatterjea Publication where species C is only produced in a minor amount. This was exemplified a 90% Sulfuric acid in the example of Applicant's Specification (See "preparation of 2-(n-butyl)-3-carboxy-5-nitrobenzofuran" ), an isolated yield of 76% is obtained for species C ("...202.5g of a beige product are obtained ... " starting from 263g of 3-(1-hydroxypentylidene)-5-nitro-3H-benzofuran-2-one A ).

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Ezamville(France).

Date: 29<sup>th</sup> August 2008

Alain Schouteeten